PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference p21	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/NL2004/000650	International filing date *(day/month/year)* 20.09.2004	Priority date *(day/month/year)* 19.09.2003

International Patent Classification (IPC) or national classification and IPC
A23L1/29, A23L1/09, A23L1/305, A23L1/30

Applicant
N.V. NUTRICIA et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.09.2005	08.02.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2004/000650

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-26 as originally filed

Claims, Numbers

1-18 received on 30.09.2005 with letter of 26.09.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2004/000650

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item IV

The separate inventions/groups of inventions are:

1,2,5-10 (partially), 11,12, 15-18 (partially)
use of water soluble carbohydrate in the manufacture of a composition for use in a method of preventing multiple organ dysfunction in a mammal suffering from trauma and composition according to claim 11 comprising:
20-200g/l digestible dissolved carbohydrate
5-5000 mg/l guanosine equivalents
at least one of 1-100g/l ribose equivalents and 2-2000mg flavonoids and
45-97.95% water.

3,4,5-10 (partially),13,14,15-18 (partially)
use of water soluble carbohydrate in the manufacture of a composition for use in a method of preventing multiple organ dysfunction in a mammal suffering from trauma and composition according to claim 13 comprising:
20-200g/l digestible dissolved carbohydrate
0.01- 10 mM of peptides with ACE inhibiting activity, said peptides exhibiting an IC-50 concentration of less than 1000 microM and
45-97.95% water.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The special technical feature linking inventions 1 and 2 is a combination of 20-200g/l digestible dissolved carbohydrate and 45-97.95% water in a preoperative nutritional formulation.

Such combination is however not novel (see e.g. claim 1 of US 5 438 043 which discloses a preoperative drink comprising between 80 and 200 g/l digestible carbohydrate and water, the amount of water necessarily falls in the range of present claim 1).

The inventions 1 and 2 are therefore not linked by a special technical feature defining a

contribution over the prior art in the sense of Rule 13(2) PCT, the application hence lacks unity within the meaning of Rule 13(1) PCT.

Re Item V

1 Reference is made to the following documents:

D1 : US 5 438 043 A (LJUNGQVIST ET AL) 1 August 1995 (1995-08-01)
D2 : EP 0 875 155 A (N.V. NUTRICIA) 4 November 1998 (1998-11-04)
D3 : US 5 602 109 A (MASOR ET AL) 11 February 1997 (1997-02-11)
D4 : US 2002/183263 A1 (HAGEMAN ROBERT JOHAN JOSEPH ET AL) 5 December 2002 (2002-12-05)
D5: WO 03/074129 A (GLANBIA FOODS, INC; WARD, LOREN, S; BASTIAN, ERIC, D; PAULSEN, STARLA,) 12 September 2003 (2003-09-12)

2 Document D1, which is considered to represent the most relevant state of the art concerning the subject-matter of claims 1 and 3 discloses (the references in parentheses applying to this document): the use of digestible carbohydrate in the manufacture of a composition to improve post operative metabolism. The composition neither contains guanosine or guanosine equivalent nor ribose or ribose equivalent or peptides with ACE-inhibiting properties.

Document D2, discloses (the references in parentheses applying to this document): a liquid nutritional composition for enteral peri-operative use comprising soluble carbohydrate and glutamine or a glutamine precursor. The composition neither contains guanosine or guanosine equivalent nor ribose or ribose equivalent or peptides with ACE-inhibiting properties.

2.1 The subject-matter of claims 1 and 3 is therefore novel (Article 33(2) PCT)
The problem to be solved by the present invention may be regarded as: providing an improved nutritional composition to reduce the incidence of multiple organ dysfunction (MOD) following trauma.

2.2 The solution to this problem proposed in claims 1 and 3 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: Neither D1 nor D2 suggest the use of guanosine or guanosine equivalent, ribose or ribose equivalent or peptides with ACE-inhibiting properties in the amounts specified in claims 1 and 3 to solve the above problem.

A composition comprising soluble carbohydrates and guanosine is known e.g. from D3, (see passages cited in the search report), however the compositions of D3 are not used for the purpose of preventive multiple organ dysfunction in a mammal suffering form trauma. The use of water soluble carbohydrate in combination with guanosine or ribose (or equivalents thereof) in the manufacture of a composition for preventing MOD in a mammal suffering from trauma could hence not be inferred from D3.

3 Document D4, discloses (the references in parentheses applying to this document): a rehydration drink containing inter alia g/l yeast extract (comprising guanosine), g/l (D)-ribose and g/l maltodextrin.

From this, the subject-matter of independent claim 11 differs in that: the composition contains at least 20 g/l dissolved carbohydrates.

The subject-matter of claim 11 is therefore novel (Article 33(2) PCT)

The problem to be solved by the present invention (as claimed in claim 11) may be regarded as: providing an improved nutritional composition to reduce the incidence of multiple organ dysfunction (MOD) following trauma.

3.1 The solution to this problem proposed in claim 11 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: the compositions of D4 are not directed to the purpose of preventing multiple organ dysfunction in a mammal suffering form trauma. It would hence not be obvious to a person skilled in the art to take D4 as a starting point or even as a relevant teaching in the formulation of a composition suitable to solve the above problem.

4 The subject matter of claims 13-18 is not disclosed in D5.

The document D5 (see examples) discloses aqueous liquid compositions or dry mix comprising at least 20g/l of digestible water soluble carbohydrate and ACE-inhibiting peptide components. D5 does not disclose however compositions comprising in addition to the above components either guanosine equivalents, ribose equivalents, folic acid equivalents or flavonoids.

D5 is directed to compositions and methods for treatment of body weight conditions. The problem underlying the present invention being to provide an improved nutritional composition to reduce the incidence of multiple organ dysfunction (MOD) following trauma, D5 cannot be considered as a starting point or even as a relevant teaching in the formulation of a composition suitable to solve the above problem.

It would hence not be obvious to modify the compositions according to D5 or any other documents from the available prior art, to obtain the compositions in accordance with claims 13-18.

CLAIMS

1. Use of digestible water soluble carbohydrates and a liver guanosine-5'-triphosphate (GTP) increasing component in the manufacture of an aqueous liquid composition for use in a method of preventing multiple organ dysfunction in a mammal suffering from trauma, said method comprising enterally administering to said mammal, within 24 hours of the occurrence of the trauma, (i) the liver GTP increasing component selected from the group consisting of: 2-2000 mg guanosine equivalents; 0.5-40 g ribose equivalents; and combinations thereof and (ii) at least 20 g of the digestible water soluble carbohydrates in the form of an aqueous liquid composition containing at least 10 g/l of said digestible water soluble carbohydrates.

2. Use according to claim 1, wherein the method comprises administering, within 24 hours of the occurrence of the trauma, 0.05-100 mmole of peptides with Angiotensin Converting Enzyme (ACE) inhibiting activity, said peptides exhibiting an IC-50 concentration as defined in the specification of less than 1000 μM.

3. Use of digestible water soluble carbohydrates and peptides with ACE inhibiting activity in the manufacture of an aqueous liquid composition for use in a method of preventing multiple organ dysfunction in a mammal suffering from trauma, said method comprising enterally administering to said mammal, within 24 hours of the occurrence of the trauma, (i) 0.05-100 mmole of peptides with ACE inhibiting activity, said peptides exhibiting an IC-50 concentration as defined in the specification of less than 1000 μM and (ii) at least 20 g of the digestible water soluble carbohydrates in the form of an aqueous liquid composition containing at least 10 g/l of said digestible water soluble carbohydrates.

4. Use according to claim 3, wherein the method comprises administering, within 24 hours of the occurrence of the trauma, a liver GTP increasing component selected from the group consisting of: 2-2000 mg guanosine equivalents; 0.1-10 g folic acid equivalents; 0.5-40 g ribose equivalents; and combinations thereof.

5. Use according to any one of the preceding claims, wherein the trauma is surgery, preferably prescheduled surgery.

6. Use according to any one of the preceding claims, wherein the liquid composition is administered prior to the occurrence of the trauma.

7. Use according to any one of the preceding claims, wherein the liquid composition contains between 30 and 200 g/l of digestible polysaccharides.

8. Use according to any one of the preceding claims, wherein the digestible water soluble carbohydrates are selected from the group consisting of dextrins, maltodextrins, starches, dextran and combinations thereof.

9. Use according to any one of the preceding claims, wherein the method comprises enterally administering, within 24 hours of the occurrence of the trauma, at least 50 g of the digestible water soluble carbohydrates in the form of the aqueous liquid composition.

10. Use according to any one of the preceding claims, wherein the method comprises administering, within 24 hours of the occurrence of the trauma, 2-2000 mg guanosine equivalents.

11. An aqueous liquid composition suitable for enteral administration containing:

- 20-200 g/l digestible dissolved carbohydrates;
- 5-5000 mg/l guanosine equivalents;
- at least one of 1-100 g/l ribose equivalents and 2-2000 mg/l flavonoids; and
- 45 to 97.95 wt.% water.

12. Aqueous liquid composition according to claim 11, containing 5-5000 mg/l guanosine equivalents and at least 1-100 g/l ribose equivalents.

13. An aqueous liquid composition suitable for enteral administration containing:

- 20-200 g/l digestible dissolved carbohydrates;
- 0.01 to 10 mM of peptides with ACE inhibiting activity, said peptides exhibiting an IC-50 concentration of less than 1000 μM; ~~and~~
- at least one of:
  - 5-5000 mg/l guanosine equivalents
  - 1-100 g/l ribose equivalents

- o 0.2 and 400 mg/l folic acid equivalents
- o 2-2000 mg/l flavonoids; and
- 45 to 97.95 wt.% water.

14. Liquid composition according to claim 13, wherein the composition contains 5-5000 mg/l guanosine equivalents and/or 1-100 g/l ribose equivalents.

15. Liquid composition according to any one of claims 11-14, the composition contains between 0.2 and 400 mg/l folic acid equivalents.

16. Liquid composition according to any one of claims 11-15, wherein the composition contains flavonoids in a concentration within the range of 2-2000 mg/l.

17. An aqueous liquid composition according to claim 11 or 12, or an aqueous liquid composition suitable for enteral administration containing:

- 20-200 g/l digestible dissolved carbohydrates;
- 0.01 to 10 mM of peptides with ACE inhibiting activity, said peptides exhibiting an IC-50 concentration of less than 1000 μM; and
- 45 to 97.95 wt.% water.

~~17. Liquid composition according to any one of claims 11-16,~~ wherein the liquid composition is a clear aqueous solution.

18. A composition that can be reconstituted with water to a liquid composition according to any one of claims 11-17.